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## ORIGINAL RESEARCH ARTICLE

# Risk of Falling and Hypnotic Drugs: Retrospective Study of Inpatients

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## Abstract

**Background** Falls and related injuries remain a concern for patient safety in many hospitals and nursing care facilities. In particular, reports examining the relationship between accidents and drugs with a sedative effect have been increasing; however, the analysis of correlation between the background factors of fall accidents and the detailed therapeutic category of drugs is insufficient.

**Objectives** Our objective was to estimate fall risk following the administration of hypnotics in inpatients within an acute hospital. We assessed the relationship between falls and hypnotic drugs compared with other medicines.

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**Study Design and Setting** An inpatient population-based study was carried out at Gunma University Hospital, where all inpatients admitted between 1 October and 31 December 2007 were included. Over a 3-month follow-up period, all reports of falling accidents from ward medical staff were investigated.

**Results and Discussion** Falls occurred in 1.8 % of males and 1.3 % of females in the study population ( $n = 3,683$ ). The mean age of patients who experienced falls ( $64.7 \pm 19.5$  years) was significantly higher than that of patients who did not ( $56.2 \pm 20.2$  years). Multivariate analysis revealed the following drugs as high-risk factors for falling: hypnotics (odds ratio [OR] 2.17, 95 % CI 1.44–3.28), antiepileptics (OR 5.06, 95 % CI 2.70–9.46), opioids (OR 3.91, 95 % CI 2.16–7.10), anti-Alzheimer's (OR 5.74, 95 % CI 1.62–20.3), anti-Parkinson's (OR 5.06, 95 % CI 1.58–16.24), antidiabetics (OR 3.08, 95 % CI 1.63–5.84), antihypertensives (OR 2.24, 95 % CI 1.41–3.56), and antiarrhythmics (OR 2.82, 95 % CI 1.36–5.86). Multivariate logistic regression analysis of hypnotics, brotizolam, zopiclone, and estazolam revealed a significant association with an increased risk of inpatient falling accidents, while zolpidem, triazolam, flunitrazepam, and nitrazepam did not.

**Conclusion** The present findings suggest that the risk of falling accidents in hospitals differs according to the type of hypnotic drug administered. The appropriate selection of hypnotic drugs, therefore, might be important for reducing the number of patient falls.

## 1 Background

Injuries due to falls remain a concern for inpatient safety. According to the newest Cochrane database, approximately

30 % of people aged over 65 years living in the community fall each year [1]. Fall incidence in nursing homes is reported to be about three times that in the community, equating to rates of 1.5 falls per bed per year (range 0.2–3.6) [2, 3]. In hospital, on the other hand, an incidence of 3.4 falls per person-year has been reported in geriatric rehabilitation wards, and 6.2 falls per person-year in psychogeriatric wards [4, 5]. In spite of more intense risk management, the high number of accidental falls in hospital is a severe problem.

Several studies have demonstrated that some kinds of medications contribute to falls [1, 2, 4]. Benzodiazepines and hypnotics [6–9], antidepressants [10–12], anti-hypertensives and diuretics [13, 14], narcotics [8], and anti-Parkinson's [15] drugs are reported as risk factors of falls. We began to investigate the association between accidental falls and medication in wards, and we found that only zolpidem, the  $\omega_1$ -selective non-benzodiazepine, showed the lowest odds ratio (OR) of falls in hypnotics tested.

Hypnotic drugs are frequently used for insomnia (with symptoms such as difficulty falling asleep or staying asleep, awaking too early in the morning, and disturbance in sleep quality), and they may cause falls because of their effect on psychomotor activity. Therefore, appropriate selection of hypnotics and assessing the related risks might be important in the prevention of accidental falls. Short-acting non-benzodiazepines are known to be relatively safe hypnotics and are widely used to treat difficulty in falling asleep. In 1999, Rudolph et al. [16] reported that the myorelaxant, motor-impairing, ethanol-potentiating, and anxiolytic-like properties of diazepam were not mediated by  $\alpha 1$  gamma-aminobutyric acid (GABA)<sub>A</sub> receptors, but might be mediated exclusively by  $\alpha 2$ ,  $\alpha 3$ , and/or  $\alpha 5$  GABA<sub>A</sub> receptors. In 2008, Hanson et al. [17] reported that in cases of sedative/hypnotic activity of benzodiazepine receptor [BZ ( $\omega$ )] agonists, determined by the ratio of selectivity in  $\omega 1/\omega 2$  receptor subtypes, the difference in  $\omega 1/\omega 2$  selectivity may lead to a difference in falling probability. However, the association between falling related to taking hypnotics and the  $\omega 1/\omega 2$  selectivity of each hypnotic was not clearly established.

In this study, we assessed the falling frequency of inpatients admitted to a ward of Gunma University Hospital, to clarify the association between the risk of falling and the medication, particularly hypnotics.

## 2 Methods and Study Design

Gunma University Hospital is a general hospital with 725 beds in 15 medical departments. This study included all hospitalized patients; there were no exclusion criteria regarding disease or age. Medical records were obtained from 3,683 unrelated Japanese hospitalized patients (1,965

males and 1,718 females; mean age  $56.5 \pm 18.6$  years) from October to December 2007 at Gunma University Hospital. Medical record analysis was approved by the Ethical Review Board in Gunma University Hospital. Inpatient falls are regularly registered via incident and accident reports submitted by medical staff. Falls were evaluated according to a previous report by Gibson [18], and medical charts were reviewed to obtain inpatient data. All drugs prescribed for the patients during their stay in hospital were extracted electronically from hospital charts. The frequency of falling was compared among drugs classified as hypnotics, antiepileptics, opioids, anti-Alzheimer's, anti-Parkinson's, antipsychotics, antidiabetics, antihypertensives, and antiarrhythmics, according to the therapeutic category of drugs defined by the Japanese Ministry of Health and Labor Welfare.

## 3 Statistical Methods

The medical staff in the ward (nurses, pharmacists, and medical doctors) who found the fall accident or was informed about one by a patient completed an incident sheet. The data were calculated as the number of patients who experienced one fall divided by the total number of inpatients. The Student's *t* test was used for comparison of age, and a chi-square analysis was used for comparison of sex difference. The relationship between medication and the prevalence of falls was estimated by comparing the odds of exposure among patients who fell during hospitalization. A logistic regression analysis with a stepwise procedure was used to identify the independent risk factors of falling as reported by Tanaka et al. [19]. The OR and corresponding 95 % confidence interval (CI) were calculated using logistic regression in StatView (SAS, Cary, NC, USA) software. Finally, a multiple logistic regression analysis, adjusted for use of diuretics and anticoagulants was performed to evaluate the odds of falling for each drug. The full model included age and the use of zolpidem, brotizolam, zopiclone, triazolam, flunitrazepam, nitrazepam, estazolam, antiepileptics, opioids, anti-Alzheimer's, anti-Parkinson's, antidiabetics, antihypertensives, and antiarrhythmics. The relationship between OR and  $\omega 1/\omega 2$  selectivity reported previously [20–42] was explored using linear regression analysis. Statistical significance was set at  $p < 0.05$ .

## 4 Results

### 4.1 Characteristics of Patients and Fall Rate

Falling accidents were reported for 116 (3.1 %) of the 3,683 inpatients during hospitalization. Mean age on

admission was  $56.5 \pm 20.2$  years. The age of inpatients experiencing a fall ( $64.7 \pm 19.5$ ) was significantly higher ( $p < 0.001$ , Student's  $t$  test) than those who did not fall ( $56.2 \pm 20.2$ ). In male patients, the proportion experiencing a fall (67/116, 57.8 %) did not differ from those who did not fall (1,898/3,567 [53.2 %];  $p = 0.33$ , Chi-square test).

#### 4.2 Falling Risk of Medication

Multiple logistic regression analysis showed a significant relationship between risk of inpatient falls and several drug groups, such as hypnotics, antiepileptics, opioids, anti-Alzheimer's, anti-Parkinson's, antidiabetics, antihypertensives, and antiarrhythmics (Table 1). Sex and antipsychotics were not risk factors for falling. In the analysis adjusted for use of diuretics and anticoagulants, brotizolam, zopiclone, and estazolam showed a significant increase in the risk of inpatient falls ( $p < 0.001$ ,  $p = 0.011$  and  $0.013$ , respectively), while zolpidem, triazolam, flunitrazepam, and nitrazepam did not show any difference ( $p = 0.315$ ,  $0.416$ ,  $0.327$ , and  $0.446$ , respectively) (Table 2).

### 5 Discussion

Risk factors for falls have been reported [43, 44] to include age, sensorial impairments, various pathologies (e.g., anemia, neoplasms, congestive heart failure, and stroke); environmental and staff conditions; gait instability; limb weakness; urinary incontinence, frequency, or need for assisted toileting; agitation; confusion; impaired judgment;

and prescription of high-risk drugs, such as sedative hypnotics. Barbiturates and benzodiazepines promote sleep by binding to and allosterically modulating GABA<sub>A</sub> receptors in the central nervous system. However, these drugs have been associated with several adverse reactions, including alteration of sleep architecture, nightmares, agitation, confusion, lethargy, withdrawal, and a risk of dependence and abuse. The newest generation of sleep-aid drugs, the non-benzodiazepine hypnotics such as zolpidem, was developed to overcome some of these disadvantages [45].

In this study, only zolpidem, the most  $\omega 1/\omega 2$ -selective agent, showed an OR of  $<1$  (Table 2). Non-benzodiazepine drugs, including zolpidem, act through a similar neural mechanism as classical benzodiazepines. They bind to the same site on the GABA<sub>A</sub> receptors but differ significantly in their chemical structure and neuropharmacological profile [46–48]. GABA<sub>A</sub> receptors have a pentameric form comprising 19 subunits ( $\alpha 1$ -6,  $\beta 1$ -3,  $\gamma 1$ -3,  $\delta$ ,  $\epsilon$ ,  $\theta$ ,  $\pi$ , and  $\rho 1$ -3) [24, 49, 50]. The benzodiazepine binding site is now known to be associated with  $\alpha$  and  $\gamma$  subunits. The pharmacologically defined benzodiazepine receptor subtype BZ1 ( $\omega 1$ ) seems to correspond to the GABA<sub>A</sub> receptors containing  $\alpha 1$  subunits, whereas the BZ2 ( $\omega 2$ ) subtype is heterogeneous and corresponds to GABA<sub>A</sub> receptors with  $\alpha 2$ ,  $\alpha 3$ , or  $\alpha 5$  subunits [51, 52]. GABA<sub>A</sub> receptors containing different  $\alpha$  subunits show a heterogeneous distribution in the brain, and it has been suggested that different receptor subtypes may have different functional roles [53]. In case of sedative and hypnotic activity of BZ ( $\omega$ ) agonists, determined by the ratio of selectivity in  $\omega 1/\omega 2$  receptor subtypes, the difference in  $\omega 1/\omega 2$  selectivity may influence the difference in falling probability [17].

**Table 1** Relationship between fall frequency and selected variables in hospitalized patients

Variable	All inpatients (% of total)	Falls (% of total)	Non-falls (% of total)	Multivariate adjusted <sup>a</sup>		<i>p</i> value
				OR	(95 % CI)	
Sex						
Male	1,965 (53.4)	67 (1.8)	1,898 (51.5)			
Female	1,718 (46.6)	49 (1.3)	1,669 (45.3)	0.95	(0.63–1.43)	0.806
Total	3,683 (100)					
Age				1.02	(1.01–1.04)	0.001
Hypnotics	1,306 (35.5)	92 (2.5)	1,214 (33.0)	2.17	(1.44–3.28)	<0.001
Antiepileptics	108 (2.9)	17 (0.5)	91 (2.5)	5.06	(2.70–9.46)	<0.001
Opioids	163 (4.4)	22 (0.6)	141 (3.8)	3.91	(2.16–7.10)	<0.001
Anti-Alzheimer's	15 (0.4)	6 (0.2)	9 (0.2)	5.74	(1.62–20.3)	0.007
Anti-Parkinson's	27 (0.7)	6 (0.2)	21 (0.6)	5.06	(1.58–16.2)	0.006
Antipsychotics	327 (8.9)	33 (0.9)	294 (8.0)	1.34	(0.79–2.26)	0.273
Antidiabetics	111 (3.0)	15 (0.4)	96 (2.6)	3.08	(1.63–5.84)	<0.001
Antihypertensives	382 (10.4)	35 (1.0)	347 (9.4)	2.24	(1.41–3.56)	<0.001
Anti-arrhythmics	82 (2.2)	11 (0.3)	71 (1.9)	2.82	(1.36–5.83)	0.005

<sup>a</sup> Adjusted for use of diuretics and anticoagulants  
CI confidence interval, OR odds ratio

**Table 2** Relationship between hypnotics and selected variables of fall frequency in hospitalized patients

Variable	All inpatients (% of total)	Falls (% of total)	Non-falls (% of total)	Multivariate adjusted <sup>a</sup>		<i>p</i> value
				OR	(95 % CI)	
Age				1.02	(1.01–1.04)	0.002
Hypnotics						
Zolpidem	382 (10.4)	11 (0.3)	371 (10.1)	0.698	(0.35–1.41)	0.315
Brotizolam	696 (18.9)	52 (1.4)	644 (17.5)	2.436	(1.61–3.68)	<0.001
Zopiclone	40 (1.1)	8 (0.2)	32 (0.9)	3.773	(1.36–10.4)	0.011
Triazolam	82 (2.2)	7 (0.2)	75 (2.0)	1.466	(0.58–3.68)	0.416
Flunitrazepam	46 (1.2)	4 (0.1)	42 (1.1)	1.758	(0.57–5.44)	0.327
Nitrazepam	29 (0.8)	5 (0.1)	24 (0.7)	1.656	(0.45–6.07)	0.446
Estazolam	31 (0.8)	5 (0.1)	26 (0.7)	4.027	(1.35–12.1)	0.013
Antiepileptics	108 (2.9)	17 (0.5)	91 (2.5)	4.594	(2.43–8.70)	<0.001
Opioids	163 (4.4)	22 (0.6)	141 (3.8)	4.622	(2.66–8.03)	<0.001
Anti-Alzheimer's	15 (0.4)	6 (0.2)	9 (0.2)	5.386	(1.45–20.1)	0.012
Anti-Parkinson's	27 (0.7)	6 (0.2)	21 (0.6)	4.707	(1.34–16.5)	0.016
Antidiabetics	111 (3.0)	15 (0.4)	96 (2.6)	3.101	(1.64–5.88)	<0.001
Antihypertensives	382 (10.4)	35 (1.0)	347 (9.4)	2.175	(1.36–3.48)	0.001
Anti-arrhythmics	82 (2.2)	11 (0.3)	71 (1.9)	2.948	(1.42–6.14)	0.006

<sup>a</sup> Adjusted for use of diuretics and anticoagulants  
*CI* confidence interval, *OR* odds ratio

Another possible reason for the variance in the risk of falls is the difference in the pharmacokinetics of hypnotics. Zolpidem has the shortest elimination half-life and carries the lowest risk of falling. The maximum plasma concentration of zolpidem is reached 1.5 h after dosing [30]. A shorter time to reach peak concentration and a short elimination half-life may be preferable characteristics for hypnotic agents. A considerable number of accidental falls occur when a patient wakes because of a micturition urge during night. Thus, for patients with insomnia, it is important to select a hypnotic with a short half-life to avoid excessive suppression of psychomotor activity after sleeping.

Finally, low-risk drug–drug interactions could explain the low frequency of falls in patients taking zolpidem. Although the formation of alcohol derivatives of zolpidem is rate-limiting and mediated principally by cytochrome P450 (CYP)3A4 (about 60 %), the rest is metabolized by CYP1A2, CYP2C9, CYP2C19, and CYP2D6 [54, 55]. Such metabolic profiles could reduce the risk of drug–drug interaction and genetic polymorphism compared with other hypnotics, such as triazolam, which is metabolised by only CYP3A4 [56, 57]. The difference in metabolic profiles may contribute to the low risk of falling with zolpidem, even when patients are concurrently administered several drugs that inhibit the metabolic pathway of zolpidem. This is especially valid for elderly patients, most of whom receive polytherapy, which increases the risk of drug–drug interaction. Consequently, genetic analysis may be a useful tool for the prevention of falls related to medications, particularly hypnotics.

In this study, we evaluated the association of falling with medication but not the medical conditions or disease of patients. Although we clarified the difference in the risk of falling among hypnotics, in future, we should also establish the relationship between the time when falls occur, drug dosage, and medical condition or disease.

## 6 Conclusion

Our results show that many falls depend on the type of hypnotic agent in inpatients with insomnia. In order to clarify the correlation between each hypnotic and the risk of falling, it is still necessary to evaluate the time of taking drugs and falling accident. Falls are a common risk for all inpatients. Reduction in the number of falls and related injuries is important for maintaining patient quality of life and for reducing medical costs. However, the risk of falls is not able to be predicted from  $\omega$ 1/ $\omega$ 2 selectivity. The relationship between falling and the profiles of various hypnotics remains to be analyzed.

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